

SENTINEL LYMPH NODE BIOPSY IN SURGICAL STAGING OF ENDOMETRIAL CARCINOMA

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Endometrial carcinoma is the most common gynecologic malignancy. There has been a steady increase in incidence over latter decades, in large part due to the global obesity pandemic and aging population [1-4]. The majority of women with endometrial carcinoma present at an early stage, with disease confined to the uterus. It is well accepted that surgical staging should include hysterectomy and bilateral salpingo-oophorectomy. However, the role and extent of lymph node dissection is highly debated [5-12]. Evidence suggests that lymphadenectomy provides prognostic information and directs the use of appropriate adjuvant treatment in patients who are node-positive. Furthermore, it eliminates the need for adjuvant treatment in low-risk patients with negative nodes and no extrauterine spread of disease. Since lymphadenectomy has not been associated with improved survival for women with apparent early-stage endometrial carcinoma [2,3], and carries risks of intra- and postoperative complications [4], sentinel lymph node (SLN) biopsy has emerged as an alternative staging approach thought to reduce potential complications associated with lymphadenectomy whilst still providing accurate staging [1].

Three injection sites were mainly used: the uterine fundus, the endometrium using hysteroscopy, and the cervix [3]. The fundal injection site was not associated with high detection rates, and it is often not technically feasible when there is distortion of the uterus secondary to leiomyomas, which is not an uncommon occurrence [9]. The hysteroscopic approach focused on a peritumoral injection concept and involved identifying the tumor by direct visualization and injecting the underlying endometrium. The initial published reports with this approach were encouraging, indicating a high rate of detection in both the pelvic and aortic nodal areas mimicking the distribution of lymph node metastasis [10, 11]. Despite these encouraging initial results, however, this technique has not been widely adopted. Compared with the other injection methods, this is a

technically more involved approach (hysteroscopic visualization of the tumor and the surrounding endometrium is not easy when the tumor is either too large and occupying the whole endometrial cavity, or too small/microscopic and harder to identify) and frequently involves a separate procedure the day before the hysterectomy, ultimately creating a logistical challenge and understandably minimal enthusiasm from patients [6]. The third injection approach, which has gained the most popularity in recent years, involves injection into the cervix. The cervix is almost always clearly visualized and accessible despite major distortion of the uterine corpus (by tumors or leiomyomas). The most recent international reports mostly use the cervix as their injection site [8,12]. With this approach, the reported SLN detection rates have surpassed 80% [3].

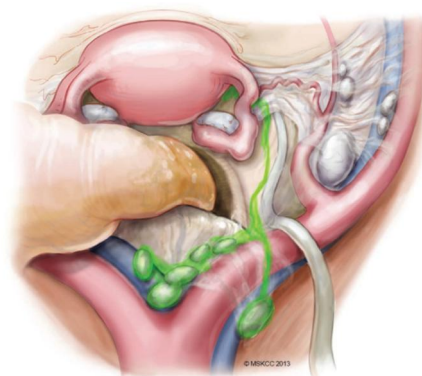


Fig 1. Most common pelvic sentinel lymph node mapping pattern following a cervical injection of dye in endometrial cancer. Lymphatic channels condense in the paracervix and emerge from the lateral uterine body and cross over the obliterated umbilical ligament to drain into the external iliac and obturator lymph nodes. This is also termed the upper or ventral paracervical pathway.

Some para-aortic lymph nodes may be reached only via the infundibulo-pelvic ligament pathway, which are not commonly accessible via the superficial cervical injection, and there is concern that some isolated para-aortic lymph node metastases are

missed due to this. This is mainly of concern in patients with high grade and deeply invasive tumors, where isolated para-aortic metastasis has been reported in as many as 16% of patients [7].

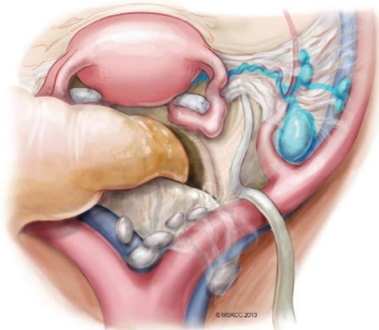


Fig 2. Less common pelvic sentinel lymph node mapping pattern following a cervical injection of dye in endometrial cancer. Lymphatic channels condense in the paracervix but do not cross over the obliterated umbilical ligament. Rather, these channels travel cephalad within the meso-ureter to drain common iliac and presacral lymph nodes. This is also termed the lower or dorsal paracervical pathway.

The main goal of the SLN approach is to identify high-yield lymph nodes, limiting the need for comprehensive lymphadenectomy. To achieve this, the technique must have a high bilateral SLN detection rate, a high sensitivity for detection of metastatic lymph nodes and a low false negative rate [11]. Multiple studies have evaluated the detection rates of SLNs in endometrial carcinoma using various tracers, alone and in combination [10]. The use of ICG (Indocyanine green) is associated with higher rates of bilateral SLN detection than blue dye. Indocyanine green is composed of small particles that exhibit diffuse fluorescence when exposed to near-infrared (NIR) excitation light ($\lambda = 600 - 900\text{nm}$) delivered by a dedicated optical system. ICG and NIR is considered the gold standard for SLN detection in women with endometrial carcinoma. The use of indocyanine green ICG is associated with a low risk of adverse effects. The risk of allergic reactions is one out of 42.000. For safety reasons, the use of ICG is contraindicated in patients with insufficient liver function and in those allergic to substances containing iodine, which is incorporated in the agent to a small fraction [1,12]. A cervical injection of dye leads to two primary drainage routes. The most common route emerges from the lateral uterine body and crosses over the obliterated umbilical ligament to drain into external iliac and obturator lymph nodes (upper or ventral paracervical pathway). The less common

pathway travels within the mesoureter cephalad to drain common iliac and presacral lymph nodes (lower or dorsal paracervical pathway). Figures 1 and 2 illustrate the two major pelvic SLN mapping patterns following a cervical injection of dye in endometrial cancer [3].

Materials and methods. Our study was including 23 patients with histologically confirmed endometrial cancer in apparently pre-operative FIGO 2011 early-stage [4,5] who underwent minimally invasive surgery. All patients signed a specific consent form and were assessed by a multidisciplinary tumor board. Sensitivity and specificity values were calculated. The pre-operative assessment included transvaginal ultrasound and magnetic resonance imaging to assess myometrial invasion. In high-risk patients, a thoracoabdominal CT was performed.

Exclusion criteria:

- Contraindication for surgical treatment
- Suspicion of metastatic disease
- Pathological pelvic or para-aortic lymph nodes in CT scan or MRI
- BMI > 45
- Story of radiotherapy in the pelvic or para-aortic regions
- Age > 80 years old (for para-aortic lymphadenectomy) or < 18 years old
- Thyroidal hyperfunction

Once general anesthesia has taken effect, the patient was placed in a dorsal lithotomy position with the arms tucked to the body. The patient was then prepped and draped. A Veres needle was inserted in the peritoneal cavity. Using a specialized 30°-laparoscope, equipped with a filter for optimal reproduction of ICG -enhanced NIR fluorescence, abdomino-pelvic organs and the peritoneal surfaces were inspected to rule out iatrogenic injuries that may have occurred during trocar insertion and to confirm the absence of extrauterine spread of disease.

Next, for cervical injection, 4 mL of diluted ICG (25 mg ICG-5 mg/mL in 10 mL sterile water) were injected at the 3 and 9 o'clock positions: 1 mL at 2 to 3 mm cervical depth and 1 mL at 10 to 15 mm depth. Once the tracer has been injected as described, a uterine manipulator was placed. Prior to gaining access to the retroperitoneal space, the camera system was switched to NIR/ICG mode to detect fluorescence which is emitted by lymphatic vessels or from an SLN. The iliac vessels were identified and the retroperitoneal space was dissected bluntly.

Blunt dissection of tissue is of utmost importance in order to minimize the risk of inadvertent disruption of lymphatic vessels and ensuing spillage of ICG solution, resulting in impaired vision during NIR/ICG mode. Inspection of the lymphoadipose tissue in the retroperitoneum was initiated in the paracervical area and proceeded laterally and cranially, following the anatomy of the cervical lymphatic drainage pathways. The parametrial tissue was inspected first, the tissue in the obturator fossa, along the external, internal and common iliac vessels, was examined subsequently. The SLN was then excised, removed and sent for histopathological analysis. The most frequent anatomical SLN locations in the pelvic area were: external iliac and obturator.

XÜLASƏ

Endometrium xərcənginin cərrahi mərhələndirməsində sentinel limf düyünlərinin biopsiyası

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Açar sözlər: endometrium xərcəngi, sentinel limfa düyünlər, yaşıl indosianin

Endometrium xərcənginin erkən mərhələsində aparılan cərrahi əməliyyatların radikallığı lazım olan həcmi əhəmiyyətli dərəcədə üstələyir. Bunu nəzərə alaraq, bugünkü gündə düzgün diaqnostika və gələcək müalicənin planlaşdırılması məqsədi ilə əməliyyat zamanı sentinel limfa düyünlərinin aşkar olunması aktual məsələlərdən hesab olunur. ICG-nin istifadəsi onu göstərir ki, sentinel limfa düyünlərinin fluoressensiya metodunun köməyi ilə aşkar olunması təhlükəsiz və effektiv diaqnostika metodu hesab olunur.

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Results. A total of 23 patients were included in the study. The median age was 61 (29-76) and median BMI - 29 (20-46). The median SLN count was 3.2 (1-6). The overall and bilateral detection rate was 95% and 86%. Sensitivity, specificity and NPV were 92.3%, 100% and 96.8% respectively per side. There were no allergic reactions to the ICG.

Conclusion. NIR fluorescence imaging with ICG is an excellent and safe tracer modality for SLN mapping with a very high overall (95%) and bilateral (86%) detection rate. Sentinel lymph node biopsy is increasingly used as an alternative to lymphadenectomy in surgical staging of women with endometrial carcinoma. The approach has gained significant acceptance and is applied in many centers [10].

РЕЗЮМЕ

Биопсия сентинелевых лимфатических узлов при хирургической стадировании рака эндометрия

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Ключевые слова: рак эндометрия, сторожевые лимфатические узлы, индоцианин зеленый

Радикальность хирургических операций, выполняемых на ранней стадии рака эндометрия, значительно превышает необходимый объем. Учитывая это, выявление сентинелевых лимфатических узлов во время операции сегодня считается одним из наиболее актуальных вопросов для правильной диагностики и планирования дальнейшего лечения. Использование ИКГ показывает, что выявление сентинелевых лимфатических узлов с помощью флуоресцентного метода считается безопасным и эффективным методом диагностики.

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